Estimating Growth Rate by a Single Measurement of Kidney Volume in ADPKD

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Autosomal dominant polycystic kidney disease (ADPKD), the most common monogenic kidney disease, is characterized by the enlargement of the total kidney volume (TKV) in an exponential and unlimited fashion, and associated with a decrease in renal function.[1] The TKV increase has been established as the primary factor determining the outcome, such as the development of end-stage renal disease.[2] Usually, the calculation of TKV increase rate and change are geometrically performed via 2 or more repeated measurements for at least 6 months, using imaging techniques, such as magnetic resonance imaging or computed tomography; however, this procedure is time-consuming and may not be readily available.[3] A mixed-model repeated-measures analysis was applied in the prospective, placebo-controlled tolvaptan efficacy and safety in the management of ADPKD and its outcomes (Tolvaptan Efficacy and Safety in Management of ADPKD and Its Outcomes [TEMPO]) 3:4 trial to reveal a treatment benefit in reducing the TKV increase rate.[4]

The TKV increase is exponential, and its model is expressed by the following equation:

$$HtTKVt = K(1 + \alpha / 100)(t - A),$$

where *HtTKV* is the height-adjusted TKV, *K* is the initial HtTKV, and *A* is the age at the start of HtTKV growth. The Mayo imaging classification (MIC), a prediction model for renal prognosis in adult patients with class 1 ADPKD, made it possible to define groups of patients with different risks of estimated glomerular filtration rate decline by a single measurement of TKV and age.[5] In MIC, subjects are stratified by an estimated increase rate α (% per year, termed as eHTKV-α) of HtTKV, derived from the following equation:

$$HtTKVt = 150(1 + \alpha / 100)t,$$

where *HtTKVt* is HtTKV at age t. Importantly, the presence of eHTKV-α individual stability is a fundamental assumption, on which the MIC is based, and if it is true, the change in eHTKV-α can be used for the assessment of individual treatment effects on HtTKV enlargement. Nevertheless, the long-term stability of eHTKV-α has not been examined yet.

Using the TEMPO 3:4 dataset for a development set and Kyorin University cohort for a validation set, Higashihara *et al.*[6] investigated the constancy of eHTKV-α, which was assumed to be stable in MIC. In placebo-assigned subjects in TEMPO 3:4, when A = 0 and K = 150, eHTKV-α fluctuated significantly from baseline during 3 years of observation. Then, they mathematically determined equation parameters A and K in HtTKV calculation at age t, as follows:

$$t = K (1 + \alpha / 100)(t - A)$$

For the determination of A, log-converted HtTKV was plotted against the age for MIC subgroups 1B through 1E in the development set, in which most of the regression lines converged in a relatively narrow area (age −5.8 to 16.1), and 0 was selected as the parameter A, although the intersection of subgroup 1E with other regression lines shifted to a negative age range. This may indicate that TKV growth began earlier in patients with a more progressive type of ADPKD. Next, the parameter K was determined by plotting the mean change in eHTKV-α from baseline to post-baseline, using A = 0 against K for 1257 TKV measurements from the development set. Moreover, at the average K-value of 133 ml/m, the plotted line intercepted 0 through the first and third year of development set and K = 130 was selected. These parameters, A = 0 and K = 130, were validated in the Kyorin University cohort and the stability was confirmed after 5 years of observation, whereas the K-value was a little smaller in the Kyorin University cohort (117 ml/m). The authors explained the difference of the K-value between the development and validation sets by lower

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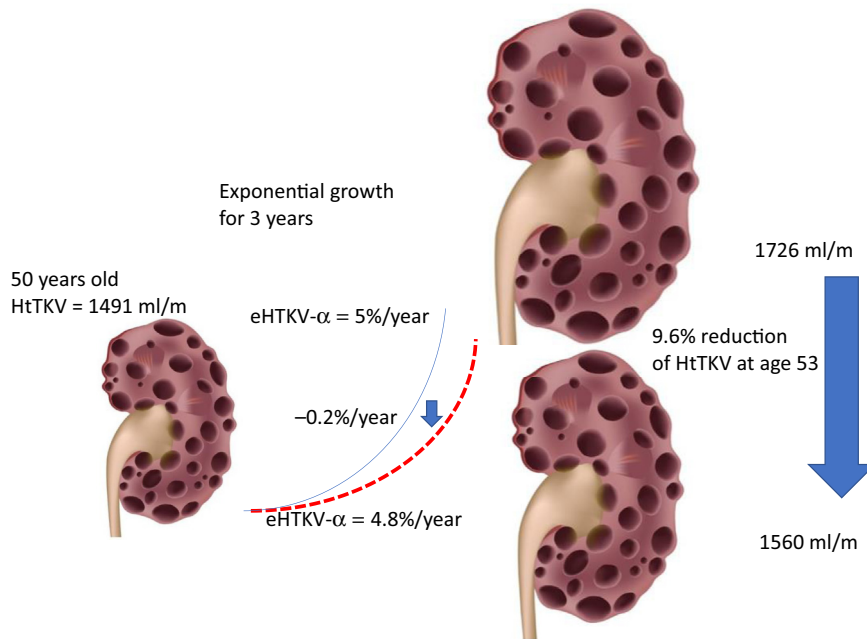
Figure 1. A simulation model of the treatment effects on total kidney volume (TKV) increase, assuming eHTKV-α is decreased 0.2% per year by tolvaptan treatment. eHTKV-α is calculated as 5% per year in a 50-year-old patient with 1491 ml of height-adjusted TKV (HtTKV). After 3 years of treatment with an effect of 0.2% per year reduction in eHTKV-α, HtTKV will be 1726 and 1560 ml/m in nontreated and treated subjects, respectively, and the reduction rate in HtTKV will be calculated as 9.6%.

K-values in subgroups at the fourth and fifth years of observation. Although the number of subjects with a longer observation period was small, this might suggest the inconsistency due to time or racial differences in eHTKV-α.

The clinical application of eHTKV-α for estimating treatment effects on TKV increase via just 1 measurement would be potentially useful. In this regard, in subjects treated with tolvaptan, eHTKV-α significantly decreased from baseline during follow-up in TEMPO 3:4. The mean change in eHTKV-α remained constant for 3 years, within a narrow range from −0.18% to −0.20% per year, whereas previous mixed-model repeated-measures analysis showed that the treatment effect of tolvaptan decreased yearly. The authors discuss that the difference in treatment effects of tolvaptan between the 2 analyses is due to the use of different control and analytical methods. A simulation was provided by the authors indicating that the 0.2% per year reduction in eHTKV-α in a patient with HtTKV = 1491 ml/m at age 50 will result in a 9.6% reduction rate in 3 years (Figure 1).

The changes in eHTKV-α in tolvaptan-treated subjects in the MIC subgroups were revealed to be larger from MIC 1B through 1E over 3 years, that is in accordance with the more substantial treatment effect observed in the recent analysis of MIC.[7] Furthermore, baseline eHTKV-α was higher in groups with a well-known risk factor for progression (men, hypertensives). These may indicate that the TKV increase rate can be calculated using a single measurement, following the proposed equation, and is a practical means to assess individual treatment effects in ADPKD.

Future studies are needed to validate the usefulness of eHTKV-α, especially using a large number of patients with varying ethnicities, at different tolvaptan doses, and with long-term follow-up.'

DISCLOSURE

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